REMARKS

Currently, claims 1, 4-6, 9-10, 16, and 94-98 are pending. Claims 2-3, 7-8, 11-15, and 17-93 have been canceled. Claims 94, 95, and 97 are withdrawn. Claim 1 is amended and finds support in previously presented claim 19. Claims 9, 10 and 96 are amended as to a matter of form. Thus, no new matter is entered. Applicants expressly reserve the right to present additional claims in further applications. All amendments and cancelations are made without prejudice or disclaimer.

Domestic and Foreign Priority

The Office Action mailed July 15, 2008 states that the translation of Foreign Priority Document is not in the file wrapper. Although public PAIR records indicate the entry of the translation, Applicants submit herewith a copy of the translation as originally filed with the USPTO on February 14, 2007.

35 U.S.C. 112, First Paragraph, Written Description

Claims 4 and 6 are rejected under 35 U.S.C. § 112 as allegedly lacking basis in the written description. Applicants respectfully disagree; however, the rejection is now mooted in light of the amendment to claim 1. Specifically, claim 1 has been amended to recite SEQ ID NO: 3. As discussed in the Office Action mailed July 15, 2008, the recitation of SEQ ID NOs: 1-3 are deemed to meet the written description requirement. As such, the rejection is obviated.

35 U.S.C. 112, First Paragraph, Enablement

Claims 5, 6, and 19 are rejected under 35 U.S.C. § 112, enablement, as allegedly being outside the scope of the enabled species. While the Applicants respectfully do not agree, the claim has been amended to recite SEQ ID NO: 3, which is enabled, according to the Office Action mailed July 15, 2008. Thus, the rejection is obviated.

35 U.S.C. § 102(e)

Claims 1, 4-6, 9, 10, 16, 19, 98 and 96 are rejected under 35 U.S.C. 102(e) as being anticipated by King et al. (U.S. Patent Publication No. 2002/0165158; hereinafter "King").

Applicants respectfully disagree; however, claim 1 and the claims dependent thereon now recite SEQ ID NO: 3. King does not disclose SEQ ID NO: 3 or how to deliver siRNA across the blood brain barrier. Therefore, the rejection is obviated.

35 U.S.C. § 103

Claims 1, 4-6, 9, 10, 16, 19, 96 and 98 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of U.S. Patent No. 5,814,620 to Robinson et al. (hereinafter "Robinson"), U.S. Patent No. 5,498,521 to Dryja et al., (hereinafter "Dryja"), Weber et al., Nucleic Acids Res. 19: 6263-6268 (1991) (hereinafter "Weber"), Epstein et al., Methods: A Companion to Methods in Enzymology 14:21-33 (1998) (hereinafter "Epstein"), Collins et al., Genomics 13 (3): 698-704 (1992) (hereinafter "Collins") U.S. Patent Publication No. 2004/0259247 to Tuschl et al., (hereinafter "Tuschl"); and Bass, Nature 411: 428-429 (2001) hereinafter "Bass." Applicants respectfully disagree while noting that claim 19 has been canceled, thereby mooting the rejection for claim 19.

The crux of the Examiner's arguments rest solely on the "equivalence" of antisense molecules and siRNA in their therapeutic use. However, the Examiner acknowledges that they are structurally distinct and, most importantly, operate via different mechanisms. The MPEP § 2183 states that a *prima facie* case for equivalence can only be found where the element "performs the function specified in the claim." As amended in the previous office action response, the claims recite that the siRNA operate via RNA interference. As admitted in the Office Action mailed July 15, 2008, antisense does not induce interference. Therefore, according to the MPEP, antisense is not an equivalent since it functions differently than siRNA because they operate differently.

Without attempting to belabor the point, the Examiner is respectfully directed to the factors that should be examined to determine equivalence according to the MPEP § 2183(A-D), none of which support a finding of equivalence:

> *(A) [Does] the prior art element perform[s] the identical function specified in the claim in substantially the same way, and produce[s] substantially the same results as the corresponding element disclosed in the specification?*
>
> Response: those of ordinary skill in the art recognize that antisense does not perform an identical function (i.e., antisense does not create RNA interference), does not operate in substantially the same way (i.e., antisense does not form a RISC silencing complex), and does not produce substantially the same

results (i.e., antisense is generally regarded as unreliable and is less effective than RNA interference).

(B) [Would] a person of ordinary skill in the art would have recognized the interchangeability of the element shown in the prior art for the corresponding element disclosed in the specification?

Response: there has been no evidence presented that antisense and siRNA are interchangeable. Simply, because siRNA and antisense can be broadly described as gene therapy does not make the molecules interchangeable, especially since they operate via different biochemical mechanisms.

(C) [Are] there insubstantial differences between the prior art element and the corresponding element disclosed in the specification?

Response: siRNA and antisense are substantially distinct in structure and operate via different biochemical mechanisms. Such differences are clearly not insubstantial.

(D) [Is] the prior art element is a structural equivalent of the corresponding element disclosed in the specification?

The structure of antisense (single stranded DNA) is obviously different than siRNA (double stranded RNA) and thus not equivalent.

Thus, antisense is not an equivalent of siRNA and the rejection is overcome.

Assuming *arguendo*, that antisense is even relevant to the discussion of siRNA, use of such antisense molecules to treat eye-disease does not render siRNA therapy obvious. Specifically, the route of delivery of siRNA is of critical importance to its use as a therapeutic. The USPTO itself acknowledges this fact in its training material on patentability of siRNA. Specifically, in a presentation to AIPLA in September of 2007, J. Douglas Shultz, an SPE of art unit 1635, stated that there is a "low expectation of success for in vivo applications [for siRNA]." *See*

http://64.233.169.104/search?q=cache:mBD31thT5hkJ:www.aipla.org/Content/Microsites101/Biotechnology/Committee_Documents3/2007_September_BCP_Meeting1/RNAiClaimTalk.ppt

(Attached as Exhibit A). Applicants have clearly overcome this low expectation of success that the USPTO acknowledges by actually delivering siRNA across the blood-brain barrier. Thus, the rejection is obviated for at least the foregoing reasons.

Furthermore, the Examiner has not addressed the art-recognized difficulty in delivering siRNA across the blood brain barrier. Instead, it is alleged that antisense inherently crosses the barrier when eye drops comprising antisense are administered. As discussed above, antisense is

not an equivalent to siRNA. Moreover, there is no evidence that the antisense actually crosses the blood-brain barrier, as pointed out in the previous Office Action response. In fact, it is recognized in the art that molecules larger than 500 Daltons are not expected to cross the blood brain barrier. *See, for example*, U.S. Patent Publication No. 20080213185. As siRNA is at least 1000 Daltons, and usually larger since it is double stranded, the art, thus, expressly teaches that such a molecule would not pass through the blood brain barrier. Therefore, absent the guidance provided by the Applicants' specification, no one of ordinary skill in the art would be motivated to even try to deliver siRNA across the blood-brain barrier, much less have any expectation of success. Thus, because there is a low expectation of success for *in vivo* use of siRNA in the first instance and an additional lack of expectation of success for molecules larger than 500 Daltons crossing the blood-brain barrier, Applicants' results are surprising the rejection is obviated.

Finally, to reiterate the arguments regarding the specific references as previously presented: Robinson discloses administration of antisense oligonucleotides to treat diseases associated with the eye, but fails to teach how to deliver these oligonucleotides past the blood brain barrier, much less how to get larger double stranded siRNA molecules past the barrier. Dryja discloses methods for diagnosing susceptibility to developing ocular disorders and the beta subunit of rod retinal cGMP phosphodiesterase, but fails to teach any methods which would be useful for treatment, much less teach how to deliver siRNA molecules past the barrier. Weber teaches the full length sequence of cGMP phosphodiesterase, but not how to use it therapeutically, much less how to deliver siRNA molecules past the barrier. Epstein discloses antisense oligonucleotides inhibitors of phosphodiesterase genes, but again not any therapeutic methods for crossing blood brain barrier or siRNA. Collins merely echoes the disclosure of Dryja and Epstein without providing any additional guidance to how to prepare a therapeutic or deliver it across the blood brain barrier. Tuschl is alleged to disclose a "complete blueprint for the design, synthesis, and use of short interfering, double stranded RNA," but fails to teach how to use it *in vivo*, much less how to induce the siRNA to cross the blood brain barrier. Finally, Bass discloses that siRNA triggers degradation of complementary mRNA, but again fails to teach how to deliver the siRNA across the blood brain barrier.

In contrast, Applicants clearly show that dsRNA can pass through the blood-retinal barrier by showing specific silencing of eGFP, Abca4 and RPE65 in retinal pigment epithelium

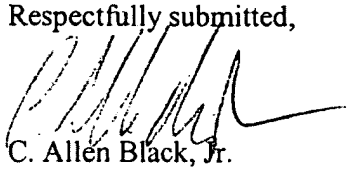
of transgenic mice through systemic administration of dsRNA targeting eGFP, Abca4 and RPE65 mRNA, respectively. Accordingly, Applicants demonstrate that dsRNA can silence expression of a target gene inside the blood-retinal barrier by delivery of a dsRNA outside the blood-retinal barrier. Based on the teachings of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass as well as what was commonly known at the time of the invention, Applicants' results should be considered surprising and unexpected. Thus, any *prima facie* case for obviousness made by the Examiner is effectively rebutted, and the Examiner's rejections based on the combined teachings of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass should be withdrawn. For at least the reasons set-forth above, reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicants' attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,



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Patenting Interfering RNA

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Exhibit A

RNAi Patentability Issues

35 U.S.C. 103 - Obviousness

- **Expectation of Success**
  - expectation of RNAi gene silencing highly likely for target sites identified as accessible to antisense inhibition (see Vickers et al. (J. Biol. Chem.) 278: 7108-7118, 2003).
    - in vitro
  - low expectation of success for *in vivo* applications.
  - High expectation of success in identifying specific modifications that are tolerated
    - Use of high-throughput assays are routine, and modification chemistry known.